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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,697	09/27/2001	Tarlochan Singh Dhadialla	A01115A (RH-0036)	4412

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RheoGene, Inc.
2650 Eisenhower Avenue
Norristown, PA 19403

EXAMINER

BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
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1649

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/965,697

Applicant(s)

DHADIALLA ET AL.

Examiner

Michael Brannock

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 April 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 3 and 13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-12 and 14-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 September 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 03/902,061102.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Claims 5 and 13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant's election with traverse of Group I, claims 1-4, 9-12, and 16-20 in the paper filed 4/7/05 is acknowledged. It is noted that claims 6-8 also read on the elected group and will thus be examined in this Office action. The traversal is on the grounds the inventions of Group I and II are not independent and distinct and that a search of Groups I and II would not be a serious burden on the examiner. This is not found persuasive for the following reasons: Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) or distinct as claimed (see MPEP § 806.05- §806.05(I)); and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. In the instant case, although a search of the two groups would overlap, the two searches would not be coextensive. Thus, Groups I and II require divergent searches, as evidenced by their separate classification, and to search both inventions would be burdensome.

Applicant's designation of the elected species, as set forth on pages 1 and 2 in the paper filed 4/7/05 is acknowledged. Applicant traverses the species election requirement on the basis

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that the examiner failed to define products with properties so distinct as to warrant separate examination and search. This argument has been fully considered but not deemed persuasive. The claims, themselves, define the distinctiveness of each of the “operable gene regulation systems” because they are required to be “orthogonal” which means that they are separate and distinct from each other, one not being required for the use of the other, as is the commonly understood meaning of the word and as defined in the specification at page 26. Moreover, Applicant has not asserted on the record that the individual species are obvious variants of each other, as suggested to Applicant in the restriction requirement (10/3/03).

Additionally, Applicant argues that it would be burden on the Applicants to choose or define only one of the 17,043 embodiments of the invention, yet Applicant also argues that a search of all of these embodiments would not be burdensome on the examiner. This argument has been fully considered but not deemed persuasive, although the examiner admits that he may not appreciate the logic behind the argument. Applicant argues that it is possible to have multiple operable gene regulation systems in a single cell and, essentially, that the claims require such. This argument has been fully considered and found persuasive to the extent that the claims require a “plurality of individually operable gene modulation systems” and thus require more than one, e.g. two. It is noted that the examiner has accepted Applicant’s elected species, as set forth on pages 1 and 2 in the paper filed 4/7/05, which comprises two individually operable gene modulation systems. Therefore the restriction is maintained and made Final.

Information Disclosure Statement

The information disclosure statement filed March 19, 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. References AG-AR were not accompanied by a legible copy. With the exception of AQ, Sambrook et al., those references have been lined through and have not been considered.

Applicant indicates that copies were not forwarded to the Patent Office because it is believed that they are too voluminous and are easily obtained by the examiner. This argument has been fully considered but not deemed persuasive. The reasons stated by Applicant do not appear to be valid or recognized reasons to disregard the requirements of 37 CFR 1.98(a)(2), see MPEP 609; never-the-less, the examiner has considered the Sambrook et al. reference because it was readily available.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 24 for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the

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following reasons: The specification makes reference to specific polynucleotide and/or polypeptide sequences, see page 17 for example; these references must contain a sequence identifier of the form: SEQ ID NO: X. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

Claims 16 recites the step of “defining a set of diversely modified ligands based on incremental pharmacophore element changes”. This step renders the metes and bound unascertainable for the following reasons:

The specification nor the claims set forth what attributes are considered “defining” as it is used in the claims. The words “diversely”, “modified” and “incremental”, as used throughout the claim, are each relative words yet the specification nor the claims have provided no distinct teaching as to when the parameters of these words are exceeded, and thus the artisan could not be reasonably sure that he or she were practicing the claimed invention.

Claim 16 recites the step of “querying the receptor polypeptides” yet the claims do not specify what questions or inquiries are meant to be encompassed by the query.

Claim 16e requires the step of determining the orthogonality of the receptor polypeptide/ligand combination to define a subset of ligands with diverse gene modulation

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properties. It is unclear what nexus there is, if any, between “determining the orthogonality of the receptor polypeptide/ligand combination” and “to define a subset of ligands with diverse gene modulation properties”. It is unclear how the first accomplishes the second. The claims are therefore indefinite as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 9-12, and 14-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cell based multiple inducible regulation systems, does not reasonably provide enablement for virally based multiple inducible regulation systems. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The claims are directed to very complex systems requiring the use of multiple and distinct expression and regulatory vectors. The art recognizes that making such a system is difficult enough using standard transfection techniques into host cells and that success with viral systems is doubtful, see Fussenegger-M, *Biotechnol. Prog.* 17(1-51)2001 who reviews the art of ecdysone responsive expression technology and concludes “The VgEcR based technology is genetically complex and requires simultaneous expression of two proteins which may complicate or prevent its use in certain viral delivery systems and autoregulatory configurations” (col 2 of page 14). Here,

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Fussenegger is discussing a single inducible regulation system, the claims claim multiples of such systems to be engineered in to a virus. No specific teachings are provided in the specification as to how this can be done, and there appears to be nothing said regarding overcoming this art recognized problem. At pages 13 and 14 the specification merely mentions a list of disparate viruses that might be used. This disclosure is simply an invitation to the skilled artisan to embark on extensive exploratory research plan to try to find-out how to make what applicant is claiming. This invitation for extensive research, with little expectation of success, does not constitute an enabling disclosure for the scope of what is claimed.

Therefore, due to the large quantity of experimentation necessary to find a way to use the invention in viruses, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the lack of expectation of success, undue experimentation would be required of the skilled artisan to make the claimed invention in its full scope.

Claims 1-4, 9-12, and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As discussed above the claims encompass viral based multiple inducible gene regulation systems, yet the specification provides no description of such nor any teaching that would enable one skilled in the art to possess such. The only examples of the claimed invention are cell based. The claims are then, in essence, single means claims.

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In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). The instant disclosure of cell based multiple inducible gene regulation systems does not put one in possession of viral based multiple inducible gene regulation systems. One skilled in the art of heterologous inducible gene regulation systems would be aware that the complexity of even the simplest of these systems argues against their use in viral systems, as reviewed by Fussenegger-M above, and would thus not recognize that Applicant was in possession of such at the time the Application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6-10, 12, 14-20 are rejected under 35 U.S.C. 102(b) as being anticipated by MORADOPOUR-D et al. Biol Chem 379(1189-1191)1998. At Col 2 of page 1189, MORADOPOUR-D et al., disclose a multiple inducible gene modulation system comprising a

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plurality of individually operable gene modulation systems wherein each individually operable gene modulation system comprises:

i) one or more polynucleotides encoding a receptor complex comprising:

A) a DNA binding domain,

B) a ligand binding domain,

C) a transactivation domain,

i.e. tTA or pVgEcR-RXR or both (as in claim 2),

ii) a ligand: i.e. tetracycline or muristerone A or both (as in claim 2)

iii) a polynucleotide comprising:

A) an exogenous polynucleotide:

B) a response element:

i.e. pUHC13 or pIND/lacZ or both (as in claim 2)

wherein the exogenous polynucleotide is operatively linked to the response element and binding of the response element in the presence of the ligand results in activation of the polynucleotide and each system is orthogonal (works independently) of the other systems (see the last paragraph of col 2 of page 1189). Furthermore, regarding claims 16-20, the procedures disclosed by MORADOPOUR-D et al. appear to read on the claims given their broadest reasonable interpretation, i.e. MORADOPOUR-D et al. defines a first set of set of polypeptide and ligands (tTA and tetracycline) a second set (pVgEcR-RXR and muristerone A) which are naturally occurring and chimeric, and expressed from cloned DNA, wherein the orthogonality of the two systems is assayed, see the last paragraph of col 2 of page 1189.

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Conclusion

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649. Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.


ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

MB



June 28, 2005